CLAIMS

What is claimed is:

1. A combinatorial library of different sequence peptide members synthesized on solid phase, where each constituent library member comprises:

(a) a peptide sequence of three or more amino acid residues bound to solid phase characterized by (i) a sequence of two or more amino acid residues forming a metal ion-binding domain and including at least one amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group, (ii) a sequence of one or more amino acid residues at the N- or C-terminus of the metal ion-binding domain, or at both the N- and C-terminus of the metal ion-binding domain, and (iii) a cleavable bond attaching the peptide sequence to solid phase; and

(b) a unique selection or sequence of amino acid residues in the peptide sequence of at least one of the constituent members of the library;

wherein the orthogonal S-protecting group may be removed without cleaving the peptide sequence from the solid phase.

2. A combinatorial library of different sequence peptidomimetic members synthesized on solid phase, where each constituent library member comprises:

(a) a peptidomimetic sequence of a combination of three or more amino acid residues and mimics of amino acid residues bound to solid phase characterized by (i) a sequence of two or more amino acid residues, mimics of amino acid residues or combinations thereof forming a metal ion-binding domain and including at least one amino acid residue or mimic of an amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group, (ii) a sequence of one or more amino acid residues, mimics of amino acid residues or combinations thereof at the N- or C-terminus of the metal ion-binding domain, or at both the N- and C-terminus of the metal ion-binding domain, and (iii) a cleavable bond attaching the peptidomimetic sequence to solid phase; and

(b) a unique selection or sequence of amino acid residues, mimics of amino acid residues or combinations thereof in the peptidomimetic sequence of at least one of the constituent members of the library;

wherein the orthogonal S-protecting group may be removed without cleaving the peptidomimetic sequence from the solid phase.

3. A combinatorial library of different sequence peptide or peptidomimetic members synthesized in solution, where each constituent library member comprises:

(a) a peptidomimetic sequence of a combination of three or more amino acid residues and mimics of amino acid residues bound to solid phase characterized by (i) a sequence of two or more amino acid residues, mimics of amino acid residues or combinations thereof forming a metal ion-binding domain and including at least one amino acid residue or mimic of an amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group, (ii) a sequence of one or more amino acid residues, mimics of amino acid residues or combinations thereof at the N- or C-terminus of the metal ion-binding domain, or at both the N- and C-terminus of the metal ion-binding domain; and

(b) a unique selection or sequence of amino acid residues, mimics of amino acid residues or combinations thereof in the peptidomimetic sequence of at least one of the constituent members of the library.

4. The combinatorial library of claim 1, 2 or 3 wherein the metal ion-binding domain further comprises at least one N available for binding to a metal ion upon removal of the orthogonal S-protecting group.

5. The combinatorial library of claim 1, 2 or 3 wherein the metal ion-binding domain comprises three residues forming an N_3S_1 ligand.

6. The combinatorial library of claim 1, 2 or 3 wherein the orthogonal S-protecting group is S-thio-butyl, acetamidomethyl, 4-methoxytrityl, S-sulfonate or 3-nitro-2-pyridinesulfenyl.

7. The combinatorial library of claim 1, 2 or 3 wherein the orthogonal S-protecting group may be removed from constituent library members thereof without otherwise altering the constituent library members or any amino acid side chain protecting group therein.

8. The combinatorial library of claim 1, 2 or 3 wherein the structural diversity occurs in the metal ion-binding domain.

9. The combinatorial library of claim 1, 2 or 3 wherein the structural diversity occurs outside the metal ion-binding domain.

10. The combinatorial library of claim 1, 2 or 3 wherein one or more constituent library members include at least one amino acid residue or mimic of an amino acid residue in the sequence at the N- or C-terminus of the metal ion-binding domain containing at least one S wherein the said S is protected by a non-orthogonal S-protecting group, whereby the orthogonal S-protecting group may be removed without removing the non-orthogonal S-protecting group.

11. The solid phase combinatorial library of claim 1 wherein the at least one amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group is an L- or D-3-mercapto amino acid, including but not limited to L- or D-cysteine or L- or D-penicillamine.

12. The combinatorial library of claim 2 or 3 wherein the at least one amino acid residue or mimic of an amino acid residue containing at least one S wherein the said S is protected by an orthogonal S-protecting group is an L- or D-3-mercapto amino acid, including but not limited to L- or D-cysteine or L- or D-penicillamine; 3-mercapto phenylananine; 2-mercaptoacetic acid; 3-mercaptopropionic acid; 2-mercaptopropionic acid; 3-mercapto-3,3,-dimethyl propionic acid; 3-mercapto-3,3,-diethyl proprionic acid; 3-mercapto,3-methyl propionic acid; 2-mercapto,2-methyl acetic acid; 3-cyclopentamethlene,3-mercaptopropionic acid; or 2-cyclopentamethlene,2-mercaptoacetic acid.

13. A method for generating a metallopeptide or metallopeptidomimetic combinatorial library, comprising the steps of:

(a) constructing a library containing a plurality of sequences of the formula Aaa-MBD-Baa cleavably bound to solid phase, wherein

(i) MBD comprises at least two amino acid residues, mimics of amino acid residues or combinations thereof, with at least one of said residues comprising at least one nitrogen atom available to complex with the coordination sphere of a metal ion, the metal ion to be provided, and with at least one of said residues comprising at least one sulfur atom protected by an orthogonal S-protecting group;

(ii) Aaa and Baa each comprise from 0 to about 20 amino acid residues, mimics of amino acid residues or combinations thereof, provided that Aaa and Baa comprise at least 1 amino acid residue or mimic of an amino acid residue, and provided that between at least two of the plurality of sequences of the formula Aaa-MBD-Baa at least either Aaa or Baa differ in at least either the sequence of residues or the selection of residues;

(b) deprotecting the sulfur atom protected by an orthogonal S-protecting group by cleaving the said orthogonal S-protecting group without cleaving the sequence from the solid phase; and

(c) complexing a metal ion to the MBD;

wherein the resulting metal ion-complexed sequences form a metallopeptide or metallopeptidomimetic combinatorial library.

14. A method for producing substantially pure metallopeptides or metallopeptidomimetics without a solution purification step, comprising the steps of:

(a) synthesizing a sequence of the formula Aaa-MBD-Baa cleavably bound to solid phase, wherein

(i) MBD comprises at least two amino acid residues, mimics of amino acid residues or combinations thereof, with at least one of said residues comprising at least one nitrogen atom available to complex with the coordination sphere of a metal ion, the metal ion to be provided, and with at least one of said residues comprising at least one sulfur atom protected by an orthogonal S-protecting group;

(ii) Aaa and Baa each comprise from 0 to about 20 amino acid residues, mimics of amino acid residues or combinations thereof;

(b) deprotecting the sulfur atom protected by an orthogonal S-protecting group by cleaving the said orthogonal S-protecting group without cleaving the sequence from the solid phase;

(c) complexing a metal ion to the MBD;

(d) cleaving the metal ion-complexed sequence from the solid phase; and

(e) recovering the resulting substantially pure metal ion-complexed sequence.

15. The method of claim 13 or 14 wherein the step of deprotecting the sulfur atom protected by an orthogonal S-protecting group is performed concurrent with the step of complexing a metal ion to the MBD.

16. The method of claim 13 or 14 wherein the step of deprotecting the sulfur atom protected by an orthogonal S-protecting group is performed prior to the step of complexing a metal ion to the MBD.

17. The method of claim 13 or 14 wherein at least one of said residues comprising at least one sulfur atom protected by an orthogonal S-protecting group is an L- or D-3-mercapto amino acid, including but not limited to L- or D-cysteine or L- or D-penicillamine; 3-mercapto phenylananine; 2-mercaptoacetic acid; 3-mercaptopropionic acid; 2-mercaptopropionic acid; 3-mercapto-3,3,-dimethyl propionic acid; 3-mercapto-3,3,-diethyl proprionic acid; 3-mercapto,3-methyl propionic acid; 2-mercapto,2-methyl acetic acid, 3-cyclopentamethlene,3-mercaptopropionic acid; or 2-cyclopentamethlene,2-mercaptoacetic acid.

18. The method of claim 13 or 14 wherein MBD comprises three residues forming an N_3S_1 ligand.

19. The method of claim 13 or 14 wherein the orthogonal S-protecting group is S-thio-butyl, acetamidomethyl, 4-methoxytrityl, S-sulfonate or 3-nitro-2-pyridinesulfenyl.

20. The method of claim 13 or 14 wherein the metal ion is V, Mn, Fe, Co, Ni, Cu, Zn, Ga, As, Se, Y, Mo, Tc, Ru, Rh, Pd, Ag, Cd, In, Sn, W, Re, Os, Ir, Pt, Au, Hg, Tl, Pb, Bi, Po, At, Sm, Eu and Gd.

21. The method of claim 13 or 14 wherein the sulfur atom protected by an orthogonal S-protecting group is cleaved without cleaving any other amino acid side chain protecting group.

22. The method of claim 13 further comprising the step (d) of cleaving the sequence from the solid phase.